

# Strong association between HLA-B\*1502 and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in mainland Han Chinese patients

Yan Zhang · Jin Wang · Li-Mei Zhao · Wei Peng · Guo-Qing Shen · Ling Xue · Xiao-Xian Zheng · Xiao-Jing HE · Chun-Yan Gong · Li-Yan Miao

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## Abstract

**Purpose** The purpose of this study is to examine the association of HLA-B\*1502 allele with CBZ-induced SJS/TEN in the mainland Han Chinese population.

**Methods** HLA-B\*1502 genotyping with sequence-specific primer polymerase chain reaction (PCR-SSP) and PCR-sequencing based typing (PCR-SBT) was performed on 17 CBZ-induced SJS/TEN patients, 21 CBZ-tolerant controls, and 185 healthy controls recruited during 2008–2010.

**Results** HLA-B\*1502 allele was present in 94.1% (16/17) of CBZ-SJS/TEN patients, 9.5% (2/21) of CBZ-tolerant patients, and 9.2% (17/185) of healthy controls. The risk of

CBZ-induced SJS/TEN was significantly higher ( $P < 0.01$ ) in the patients with HLA-B\*1502. One CBZ-induced SJS patient tested negative for HLA-B\*1502, and the test result showed HLA-B\*3503/B\*4601.

**Conclusions** We found a strong association between HLA-B\*1502 and CBZ-induced SJS/TEN in the Han Chinese population from central and northern China. Combined with previous studies of the southern Han Chinese subpopulation, our results suggest that HLA-B\*1502 is strongly associated with CBZ-induced SJS/TEN in the whole Han Chinese population.

**Keywords** HLA-B\*1502 · Carbamazepine · Stevens-Johnson syndrome · Toxic epidermal necrolysis · Mainland Chinese

Yan Zhang and Jin Wang contributed equally to this work.

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Y. Zhang · W. Peng · L. Xue · X.-X. Zheng · L.-Y. Miao (✉)  
Department of Clinical Pharmacology Research Lab,  
The First Affiliated Hospital of Soochow University,  
Suzhou, China  
e-mail: miaolysuzhou@163.com

J. Wang  
Department of Pharmacology and Laboratory of Aging  
and Nervous Diseases, Soochow University School of Pharmacy,  
Suzhou, China

G.-Q. Shen · C.-Y. Gong  
Hospital of Dermatology, Chinese Academy of Medical Sciences,  
Nanjing, China

L.-M. Zhao · X.-J. HE  
Department of Pharmacy,  
Shengjing Hospital of China Medical University,  
Shenyang, China

## Introduction

Carbamazepine is an important drug for treating seizure disorders, bipolar disorder, trigeminal neuralgia, and chronic pain. It was found to be associated with hypersensitive reactions ranging from a mild maculopapular exanthema (MPE) to life-threatening severe cutaneous reaction (SCR), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [1, 2]. Initial study [3] suggested that MHC HLA-B\*1502 allele is strongly associated with CBZ-induced SJS/TEN in subjects of Chinese/Asian ethnicity. Several follow-up studies also confirmed nearly a 100% association between HLA-B\*1502 and CBZ-induced SJS/TEN in Taiwan Han Chinese [4], Hongkong Han Chinese [5], and in the Thai population [6]. However, studies in Caucasian populations

[7] and in Japanese [8] did not find the same association. All of these studies suggested that genetic background could greatly influence the association between HLA-B\*1502 and CBZ-induced SJS/TEN. It has been found that the genetic background is different among Han Chinese in southern, central, and northern parts of mainland China [9]. Previous studies have only focused on Han Chinese or their descendents from southern China. We thought it was necessary to examine the association between HLA-B\*1502 and CBZ-induced SJS/TEN in mainland Han Chinese patients, especially those from central and northern China, before HLA-B\*1502 can be used as a prediction marker for CBZ-induced SJS/TEN.

## Methods

All subjects were recruited at the First Affiliated Hospital of Soochow University, except for three CBZ-induced SJS/TEN patients from Shengjing Hospital of China Medical University, from 2008 to 2010, following the Research Ethics Board approval of the First Affiliated Hospital of Soochow University and Shengjing Hospital of China Medical University.

CBZ-induced SJS/TEN patients were diagnosed by Roujeau's diagnostic criteria [10]. SJS was defined as skin detachment of 10% of body surface area or less, TEN was defined as skin detachment of 30% or more, and intermediate skin detachment corresponded to SJS/TEN overlap [11]. Both CBZ-tolerant patients with continuous drug usage for at least 3 months with no adverse reactions and healthy individuals without history of CBZ usage were recruited as controls. After written informed consent was obtained, peripheral blood was drawn and genomic DNA was extracted using genomic DNA purification kit (Promega, USA).

Polymerase chain reaction (PCR) using sequence specific primer (SSP-PCR) was initially employed to genotype all the subjects, according to previously published methods [5, 12–14], followed by high resolution genotyping with polymerase chain reaction sequence-based typing (PCR-SBT) for HLA-B\*1502-positive subjects.

Data are expressed as positive or negative for HLA-B\*1502. Chi-squared test and Fisher's exact test (used for alleles present in fewer than five patients or controls) were used to analyze the association between CBZ-induced SJS/TEN and HLA-B\*15 status, and *P*-values  $\leq 0.01$  were considered statistically highly significant.

## Results

HLA-B genotyping was performed on 17 CBZ-induced SJS/TEN patients, 21 CBZ-tolerant patients, and 185 healthy individuals (see "Supplemental information" for more details of patients). The frequencies of HLA-B\*1502 were 94.11% in the CBZ-induced SJS/TEN group, 9.5% in the CBZ-tolerant group, and 9.2% of the healthy patient controls (Table 1). The risk of CBZ-induced SJS/TEN was significantly higher in the patients with HLA-B\*1502 when the analysis was confined to a comparison with the CBZ-tolerant group ( $P < 0.0001$ , OR 152, 95% CI 12–1,835) and with healthy controls ( $P < 0.0001$ , OR 158, 95% CI 19–1,266). The only CBZ-induced SJS patient who tested negative for HLA-B\*1502 after PCR-SSP screening presented with HLA-B\*3503/4601 by PCR-SBT analysis.

## Discussion

In the present study, the HLA-B\*1502 allele was found in 17 of 185 healthy controls (9.2%). The frequency of the allele was consistent with previous findings in Guangdong Han [15], Taiwan Han Chinese [3], Hong Kong Han Chinese [16], but significantly different from Singapore and Japanese populations [17]. We found a strong association between HLA-B\*1502 and CBZ-SJS/TEN (94.11%), in agreement with the original study with Taiwan Chinese. The only HLA-B\*1502-negative CBZ-induced SJS patient carried HLA-B\*3503/B\*4601. It is the first time that we have found HLA-B\*4601 among CBZ-induced SJS patients in mainland Chinese. Considering the fact that ~30% Han Chinese carry HLA-B\*4601 [18], our finding doesn't suggest that HLA-B\*4601 is associated with CBZ-induced SJS/TEN in Han Chinese. HLA-B\*4601 allele was also found in CBZ-induced SJS/TEN patients in a Thai population [19], but the frequency was similar to that of the CBZ-tolerant control group, which suggests there is no significant association between HLA-B\*4601 and the Thai population. However, a related Japanese study [8] showed that B\*4601 was weakly associated with SJS in the Japanese population. Indeed, in rare cases, other HLA-B alleles were found to be associated with CBZ-induced SJS/TEN, such as HLA-B\*1558, which was found in Taiwan Han Chinese [4], and HLA-B\*1508, which was found in a homozygous Indian patient [20].

**Table 1** Characteristics and HLA-B\*1502 genotyping in each group

Group	Age (years)	Female/male ( <i>n</i> )	HLA-B*1502-positive	Total
CBZ-SJS/TEN	37.88±18.28	5/12	16	17
CBZ-tolerant	38.76±17.35	7/14	2	21
Healthy control	29.87±9.70	82/103	17	185

In conclusion, a strong association between HLA-B\*1502 and CBZ-induced SJS/TEN was found in Han Chinese from central and northern China. Combined with the previous findings, our data suggest that HLA-B\*1502 is strongly associated with CBZ-induced SJS/TEN in the whole Han Chinese population. The strength of the association suggests that HLA-B\*1502 can be used as a genetic marker to identify individuals who may be at risk for these severe adverse reactions. Therefore, an application of HLA-B\*1502 as a screening test before prescribing CBZ would be helpful in preventing CBZ-induced SJS/TEN in Han Chinese.

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